REMARKS

This responds to the Office Action mailed on August 10, 2005, and the references cited therewith.

The subject matter of claim 6 has been incorporated into claims 1 and 2. Therefore, claim 6 has been canceled without prejudice to its prosecution at another time. As a result, claims 1-5, 7 and 9-18 and 20-22 are now pending in this application.

Claims 1, 2, 7, 9, and 17 have been amended. "Thermally" has been added to claim 1 and 2. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, in claim 6 and in the Examples. The phrase "and wherein the proteinoid microsphere comprises a mixture of amino acids that are thermally condensed" has been added to claims 7, 9 and 17. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, in claim 6 and in the Examples. The phrase "and the proteinoid microsphere is stable in solution" has been added to claims 1, 2, 7, 9, and 17. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, at page 6, lines 4-6 and in the Examples. Applicant submits that no new matter has been added to the specification.

§103 Rejections of the Claims

To establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, the reference(s) must teach or suggest all the claim elements. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed modification and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

Lohrmann and Steiner

Claims 1, 2, 5 and 6 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lohrmann et al. (U.S. 6,193,953) in view of Steiner et al. (U.S. 4,925,673). The Examiner has alleged that Lohrmann discloses protein microparticles that are comprised of chemically synthesized amino acid polymers, citing to Lohrmann at col. 5, lines 40-57, and that Lohrmann discloses fluorine or radioactive iodine as a label at col. 15, lines 1-16. The Examiner further alleges that Lohrmann et al. disclose microparticles with a targeting agent such as an antibody at col. 13, lines 17-29. According to the Examiner, Lohrmann does not disclose proteinoid microspheres but this defect is cured by Steiner, which does disclose proteinoid microspheres.

Claim 1 is directed to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; wherein the label is linked to the proteinoid microsphere; and the proteinoid microsphere is stable in solution. Claim 2 is directed to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label, wherein the label is barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium, fluorine-18, carbon-11, iodine-123, technitium-99m, iodine-131, indium-111, fluorine, gadolinium, fluorescein, isothiocyalate, rhodamine, pacific blue, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde, fluorescamine, luminal, isoluminal, luciferin, luciferase or aequorin; and the proteinoid microsphere is stable in solution. Claim 5 depends from claim 1 and is directed to a labeled proteinoid microsphere synthesized for signal amplification or diagnostic imaging. Claim 6 has been canceled without prejudice to its prosecution at another time.

The Lohrmann disclosure is limited to microparticles made of proteins and, as the Examiner has stated, Lohrmann does not disclose proteinoid microspheres. Specifically, Lohrmann provides no disclosure or teaching whatsoever on proteinoid microspheres made from thermally condensed amino acids.

The Steiner disclosure is limited to disclosure of microspheres that contain pharmacological agents, where the microspheres are explicitly designed to release the

pharmacological agent in the blood, target organ or bodily fluid. See Steiner at col. 3, line 49 to col. 4, line 33.

Applicant submits first that the cited references do not teach or suggest all of the present claim elements. In particular, the combination of Lohrmann and Steiner fails to disclose labeled *proteinoid* microspheres comprising a mixture of amino acids that are thermally condensed that are *stable* enough to avoid release of an encapsulated label under a variety of different conditions. While the Examiner has alleged that Lohrmann teaches labeled *protein* microspheres such a disclosure is not a disclosure of a labeled proteinoid microsphere, particularly when combined with the Steiner reference, which explicitly focuses on *release* of a *pharmacological agents* rather than *retention* of a *label* in the proteinoid microsphere.

Applicant second submits that one of skill in the art would not be motivated to modify or combine the teachings of Lohrmann on stabilized protein microparticles with the teachings or Steiner on unstable proteinoid microspheres because there is no evidence of record that the proteinoid microspheres of Steiner have properties similar to the protein microspheres of Lohrmann. Specifically, one of skill in the art can find no teaching in Lohrmann that *proteinoid* microspheres can be substituted for protein microspheres or that *proteinoid* microspheres would have any of the same properties that Lohrmann discloses for protein microparticles (e.g., stability).

Nor would one of skill in the art have a reasonable expectation of successfully producing Applicant's invention because the combination of references does not disclose that proteinoid microspheres would be sufficiently stable in solution and under a variety of pH and other conditions to retain an encapsulated label. Contrary to the goals of Steiner, which involve releasing pharmacological agents from proteinoid microspheres, the present invention is directed to stably labeling proteinoid microspheres. Hence, the goal of the present invention would be frustrated if the teachings of Steiner were followed. Moreover, one of skill in the art would not expect that stability of the protein microcapsules would necessarily be found in a proteinoid microsphere because the bonds that are formed upon thermal condensation of amino acids are not necessarily the peptidyl (-NH-CO-) bonds that are present in proteins. As is known to one of skill in the art, while pH variations may unfold a protein, peptidyl bonds found in proteins are not necessarily cleaved under slightly basic or acidic conditions. Therefore, one of skill in the art

could not reasonably expect that simple substitution of the proteinoid microspheres of Steiner for the protein microcapsules of Lohrmann would successfully generate the present invention.

Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953) and Steiner (U.S. Patent No. 4,925,673) does not produce the claimed invention and requests withdrawal of this rejection under 35 USC § 103(a) of claims 1, 2, 5 and 6.

Lohrmann, Steiner and Mathiowitz

Claims 3 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann et al. (U.S. 6,193,953) in view of Steiner et al as applied to claims 1, 2, 5 and 6 above, and further in view of Mathiowitz et al. (U.S. Patent 5,271,961).

Claims 10 and 11 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann et al. (U.S. 6,193,953) and of Steiner et al in view of Mathiowitz et al. (U.S. Patent 5,271,961).

According to the Examiner, Mathiowitz disclose that protein microspheres can be modified by cross-linking agents such as glutaraldehyde.

Claim 3 is directed to a labeled proteinoid microsphere of claim 1 wherein the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a crosslinking agent. Claim 4 is directed to a labeled proteinoid microsphere of claim 3 wherein the crosslinking agent is carbodiimide, glutaraldehyde, N-(m-maleimidobenzoyloxy)-succinimide, a bifunctional sulfhydral reagent.

Claim 10 is directed to the labeled proteinoid microsphere of claim 7 wherein the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a crosslinking agent. Claim 11 depends from claim 10 and identifies the crosslinking agents as carbodiimide, glutaraldehyde, N-(m-maleimidobenzoyloxy)-succinimide, a bifunctional sulfhydral reagent.

Mathiowitz (U.S. Patent No. 5,271,961) is limited to disclosure of methods for making protein microspheres by solvent evaporation of a solution of proteins (not amino acids). The Mathiowitz disclosure is also limited to changing the charge on these proteins by linking amino acids to the proteins using either glutaraldehyde or carbodiimide as crosslinking agents.

Applicant submits that Mathiowitz does nothing to cure the defects of Lohrmann and Steiner. In particular, while Mathiowitz mentions glutaraldehyde or carbodiimide as crosslinking agents, it discloses only that such crosslinking agents can be used to change the charge on the proteins used for making protein microspheres. Mathiowitz does not state that proteinoid microspheres should or can be stabilized by crosslinking agents. In fact, as recited in claim 1 of the Mathiowitz disclosure, Mathiowitz explicitly teaches away from use of crosslinking agents during formation of protein microspheres. Therefore, Applicant submits that the combination of Lohrmann, Steiner and Mathiowitz does not disclose all elements of the claimed invention because even together they fail to disclose or teach proteinoid microspheres formed by thermal condensation of a mixture of amino acids in the presence of a crosslinking agent.

In addition, one of skill in the art would not be motivated to modify the teachings of Mathiowitz even when those teachings are combined with Lohrmann and Steiner for several reasons. First, Mathiowitz teaches away from using crosslinking agents during formation of the disclosed protein microspheres (see Mathiowitz claim 1). Second, Mathiowitz is limited to disclosure of *protein* microspheres, made of *proteins* (not amino acids). Third, Mathiowitz is limited to formation of microspheres by solvent evaporation or solvent extraction (not thermal condensation). And finally, Mathiowitz provides no teaching that crosslinking agents can or should be used to stabilize either proteinoid microspheres or even protein microspheres. Given these defects, Mathiowitz does not overcome the limitations of Lohrmann and Steiner, which do not disclose that proteinoid microspheres would be sufficiently stable under a variety of pH and other conditions to retain an encapsulated label. Therefore, one of skill in the art would not be motivated to modify the teachings of these references to derive the claimed invention.

Moreover, one of skill in the art would not have a reasonable expectation of successfully producing Applicant's invention from the teachings of the cited references for several reasons. First, Mathiowitz is limited to teaching that crosslinking agents are used to modify the charge of the proteins (not stabilize a microsphere). Second, Mathiowitz explicitly states that any such crosslinking should not be done *during* microsphere formation (see Mathiowitz, claim 1). And, third, Mathiowitz provides no teaching that crosslinking of amino acids during thermal condensation can successfully produce a microsphere. Given that Lohrmann and Steiner fail to

disclose that proteinoid microspheres would be sufficiently stable under a variety of pH and other conditions to retain an encapsulated label, and that Mathiowitz not only provides no methods for forming microspheres in the presence of crosslinking agents but actually states that one of skill should not form microspheres in the presence of a crosslinking agent, the skilled artisan could not reasonably expect to successfully make the present invention.

Therefore, Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673) and Mathiowitz (U.S. Patent 5,271,961) does not produce the claimed invention and requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 3, 4, 10 and 11.

Lohrmann, Steiner and Kayyem

Claims 7, 9, 12-18 and 20-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann et al. (U.S. Patent 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673) in view of Kayyem et al. (U.S. Patent 6,232,295).

Claim 7 is directed to a labeled proteinoid microsphere that is capable of binding to a specific target comprising a proteinoid microsphere linked to a label and a selective binding moiety that can bind to a specific target, wherein the label comprises a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; and wherein the proteinoid microsphere comprises a mixture of amino acids that are thermally condensed; and the proteinoid microsphere is stable in solution. Claims 12-16 depend ultimately from claim 7.

Claim 9 is directed to a labeled proteinoid microsphere that is capable of binding to a specific target comprising a proteinoid microsphere linked to a label and a selective binding moiety that can bind to a specific target, wherein the label is barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium, fluorine-18, carbon-11, iodine-123, technitium-99m, iodine-131, indium-111, fluorine, gadolinium, fluorescein, isothiocyalate, rhodamine, pacific blue, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde, fluorescamine, luminal, isoluminal, luciferin, luciferase or aequorin; and wherein the proteinoid microsphere comprises a mixture of amino acids that are thermally condensed; and the proteinoid microsphere is stable in solution.

Claim 17 is directed to a labeled proteinoid microsphere that is capable of binding to a specific target comprising a proteinoid microsphere linked to a label and an antibody that can bind to a specific target, wherein the label comprises a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; and wherein the proteinoid microsphere comprises a mixture of amino acids that are thermally condensed; and the proteinoid microsphere is stable in solution. Claims 18, 20-22 depend ultimately from claim 17.

Kayyem (U.S. Patent No. 6,232,295) is limited to disclosure of cell-specific contrast agents comprising two types of polymeric molecules, one with a net positive charge and one with a net negative charge, a cell targeting moiety and an MRI contrast agent (see Abstract). The polymeric molecule with the net negative charge is a nucleic acid. The polymeric molecule with the net positive charge can be a polycation (e.g. polylysine, col. 6, lines 39-41 and lines 55-65). The first and second polymeric molecules are preferably held together by electrostatic interactions (col. 4, lines 37-39).

Applicant submits that, like Mathiowitz, Kayyem does nothing to cure the defects of Lohrmann and Steiner. In particular, Kayyem provides no mention whatsoever of proteinoid microspheres or even microspheres and therefore does not disclose or teachings how to make stable proteinoid microspheres. Accordingly, the combination of Lohrmann, Steiner and Kayyem fails to disclose labeled *proteinoid* microspheres comprising a mixture of amino acids that are thermally condensed that are *stable* enough to avoid release of an encapsulated label under a variety of different conditions. Therefore, the combination of Lohrmann, Steiner and Kayyem fails to disclose all elements of the claimed invention.

Moreover, one of skill in the art would not be motivated to modify or combine the teachings of Lohrmann on stabilized protein microparticles with the teachings or Steiner on unstable proteinoid microspheres in view of Kayyem because Kayyem fails to disclose or teach anything whatsoever about proteinoid microspheres.

Finally, one of skill in the art would not have a reasonable expectation of successfully producing Applicant's invention from the combined teachings of these references because such a combination of references does not disclose that proteinoid microspheres would be sufficiently stable in solution under a variety of pH and other conditions to retain an encapsulated label.

Therefore, Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673) and Kayyem et al. (U.S. Patent 6,232,295) does not produce the claimed invention and respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 7, 9, 12-18 and 20-22.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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